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NUTRITION REVIEWS

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NUTRITION AND THE CANCER PROBLEM

Ten years have elapsed since a review by C. A. Baumann and the present author appeared in *Nutrition Reviews* on the nutritional aspects of the cancer problem (**4,** *353 (1946)*). A general feeling of optimism prevailed at that time about the practicability of controlling cancer formation by dietary means. This was noted both in the tone of the article and by the number of people engaged in the investigation of this problem. A special panel on nutrition was formed by the Committee on Growth of the National Research Council to consider the applications for financial support for such studies, yet two years ago this panel was combined with one on metabolism because the number of requests had gradually dwindled to such an extent that they no longer required the undivided attention of a single panel. What has happened in the intervening years to result in a diminished research effort in this field?

The control of certain types of cancer by dietary means appeared plausible ten years ago; this belief was based on two firmly established findings: the retardation of the formation of many types of tumors in animals by caloric restriction, and the inhibition of azo dye-induced hepatomas by adequate amounts of protein and riboflavin (A. Tannenbaum, *Cancer Research* **2,** *460 (1942)*; H. P. Rusch, *Physiol. Rev.* **24,** *177 (1944)*. Two of the more recent reviews on this general subject, by J. A. Miller and E. C. Miller, and by Tannenbaum and H. Silverstone, appeared in *Advances in Cancer Research* **1** *(1953) pp. 339 and 451*, respectively). It appeared to be only a matter of time until the facts gleaned from these experiments could be translated into practical use and result in the reduction of cancer incidence in the human population. Unfortunately, the problem proved to be more complex than was first realized, and so far it has not been possible to test on man the applicability of results obtained in these experimental studies.

In the opinion of the writer, there is no doubt that a drastic reduction in the incidence of almost all forms of cancer would be achieved if the caloric intake were reduced sufficiently to decrease the weight of all people to slightly below the generally accepted optimum. However, a restriction of caloric intake of such magnitude never occurs voluntarily in mankind and is observed generally only in the very poorest regions of the world or in other regions for relatively brief periods as the result of war. Since epicurean tastes are among the first to be satisfied with increasing income and since a plentiful food supply is one of the foremost goals among underdeveloped countries, it is obvious that the average person is not willing to forego the pleasure of abundant eating simply to reduce the chance of getting a neoplasm which might not occur even with gluttony.

It became apparent that a different approach to this problem was necessary, *i.e.*, the finding of some other means of attaining results similar to those obtained with caloric restriction. Vigorous exercise (H. A. Rashkis, *Science* **116,** *169 (1952)*), the reduction of environmental temperature, or the administration of dinitrophenol or of sodium fluoride (A. Tannenbaum and H. Silverstone, *Cancer Research* **9,** *403 (1949)*) will also retard the formation of several types of neoplasms in mice. However, the amount of exercise or the reduction of temperature necessary is beyond the inclinations of most people, and the administration of chemicals with such toxic properties as the ones effective in mice does not appear to be a safe solution at the present time. If we

had a better understanding of all the biochemical changes associated with caloric restriction, it might be possible to simulate this effect in some acceptable way. Although the prospect is far from imminent, it is altogether possible that a prophylactic against cancer in the form of a pill taken at regular intervals by all people over a certain age will be developed. Such measures could be expected to be especially effective against cancers that occur as the result of minimal carcinogenic stimuli.

During the past few years, a number of explanations for the retarding effect of caloric restriction on tumor genesis have been reported. W. S. Bullough (*Brit. J. Cancer* **4,** *329 (1950)*) believes that the depression of epidermal mitosis in mice which results from a limitation of caloric intake is responsible for the decreased rate of tumor formation. R. K. Boutwell, M. K. Brush, and H. P. Rusch (*Am. J. Physiol.* **154,** *517 (1948)*) have observed that mice on a low calorie diet show increased activity of the adrenal cortex and a high content of glycogen in the liver. It would appear that this increased level of glycogen arises in part from noncarbohydrate sources such as amino acids and protein. In well fed animals there are sufficient building blocks to satisfy the requirements for energy and still allow a reserve for growth, but in animals on a diet low in calories the precursors remaining for cell division are reduced to a suboptimal level, and hence tumor growth is retarded. The effect of such attrition is most noticeable during the earliest stages when the cancer nidus is minute; once the tumor mass is sufficiently large, the over-all influence of a decreased mitotic rate becomes less evident (Rusch and B. E. Kline, *Proc. Soc. Exp. Biol. Med.* **69,** *90 (1948)*).

Hepatic cancer is the most common form of neoplasm among the natives of South Africa. Inasmuch as the occurrence of this type of cancer can be reduced so effectively in rats by dietary means, it was felt that similar measures would also be effective in man, since there is good evidence that dietary inadequacies also play a major role in the formation of cancer in human beings (Rusch and Baumann, *Nutrition Reviews, loc. cit.*). Although the predominance of evidence indicates that poor diets are largely responsible for the hepatic neoplasms in Africa, it is still not possible to dismiss as an important factor the presence of certain irritating *Senecio* alkaloids which sometimes are found in the food of these people. If research on animals in the laboratory has ever furnished a lead that could alleviate cancer, it is the finding that diets adequate in protein and riboflavin will retard hepatic cancer in rats. More than ten years have passed since these facts became known, yet it has not been possible to confirm this relationship in man. The economic condition of the people and a number of other factors have complicated the purely scientific solution of this problem with numerous sociologic factors. It is of interest that a symposium on hepatic cancer, sponsored by the International Union Against Cancer, was held in Kampala and Leopoldville, Africa, in August, 1956. It is hoped that a further investigation in this field will be stimulated as a result of this meeting.

Although practicable results have not yet been achieved in the control of cancer in man by dietary means, investigations of the nutritional aspects of neoplastic growth promise again to increase during the next few years. The emphasis is shifting, however, from the influence of nutrition on the development of tumors in animals to the study of factors required for the growth of neoplastic cells in tissue culture (V. J. Evans *et al., Cancer Research* **16,** *77 (1956)*; H. Eagle, *Science* **122,** *501 (1955)*; *Nutrition Reviews* **14,** *89, 154 (1956)*; P. R. White, *J. Nat. Cancer Inst.* **16,** *769 (1955)*; A. E. Pasieka, H. J. Morton, and J. F. Morgan, *Ibid.* **16,** *995 (1956)*, and others).

The importance of defining the nutritional requirements of cancer cells cannot be overemphasized. Two important problems

are dependent on the establishment of these requirements. First, cancer cells grown in culture are now being employed as test objects for the preliminary screening of cancer chemotherapy compounds. When it becomes possible to inhibit a tumor in culture with a certain compound and to reverse the inhibition by the use of another compound, the various factors involved in growth will be more clearly established and the understanding of the mechanisms involved greatly facilitated. Second, the nutritional requirements of neoplastic cells must be carefully compared with those of other rapidly proliferating cells. If some neoplastic cells can be shown to require substances which differ from those needed by normal cells, then the more or less random selection of antimetabolites for the inhibition of tumor growth will be replaced by a specifically directed approach.

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The letters SA preceding the page number designate authors of special signed articles; the letter B designates authors of books which are listed by title in the Notes Section; LE refers to "Letters to the Editor"; N refers to articles in the Notes Section.

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had a better understanding of all the biochemical changes associated with caloric restriction, it might be possible to simulate this effect in some acceptable way. Although the prospect is far from imminent, it is altogether possible that a prophylactic against cancer in the form of a pill taken at regular intervals by all people over a certain age will be developed. Such measures could be expected to be especially effective against cancers that occur as the result of minimal carcinogenic stimuli.

During the past few years, a number of explanations for the retarding effect of caloric restriction on tumor genesis have been reported. W. S. Bullough (*Brit. J. Cancer* **4,** *329 (1950)*) believes that the depression of epidermal mitosis in mice which results from a limitation of caloric intake is responsible for the decreased rate of tumor formation. R. K. Boutwell, M. K. Brush, and H. P. Rusch (*Am. J. Physiol.* **154,** *517 (1948)*) have observed that mice on a low calorie diet show increased activity of the adrenal cortex and a high content of glycogen in the liver. It would appear that this increased level of glycogen arises in part from noncarbohydrate sources such as amino acids and protein. In well fed animals there are sufficient building blocks to satisfy the requirements for energy and still allow a reserve for growth, but in animals on a diet low in calories the precursors remaining for cell division are reduced to a suboptimal level, and hence tumor growth is retarded. The effect of such attrition is most noticeable during the earliest stages when the cancer nidus is minute; once the tumor mass is sufficiently large, the over-all influence of a decreased mitotic rate becomes less evident (Rusch and B. E. Kline, *Proc. Soc. Exp. Biol. Med.* **69,** *90 (1948)*).

Hepatic cancer is the most common form of neoplasm among the natives of South Africa. Inasmuch as the occurrence of this type of cancer can be reduced so effectively in rats by dietary means, it was felt that similar measures would also be effective in man, since there is good evidence that dietary inadequacies also play a major role in the formation of cancer in human beings (Rusch and Baumann, *Nutrition Reviews, loc. cit.*). Although the predominance of evidence indicates that poor diets are largely responsible for the hepatic neoplasms in Africa, it is still not possible to dismiss as an important factor the presence of certain irritating *Senecio* alkaloids which sometimes are found in the food of these people. If research on animals in the laboratory has ever furnished a lead that could alleviate cancer, it is the finding that diets adequate in protein and riboflavin will retard hepatic cancer in rats. More than ten years have passed since these facts became known, yet it has not been possible to confirm this relationship in man. The economic condition of the people and a number of other factors have complicated the purely scientific solution of this problem with numerous sociologic factors. It is of interest that a symposium on hepatic cancer, sponsored by the International Union Against Cancer, was held in Kampala and Leopoldville, Africa, in August, 1956. It is hoped that a further investigation in this field will be stimulated as a result of this meeting.

Although practicable results have not yet been achieved in the control of cancer in man by dietary means, investigations of the nutritional aspects of neoplastic growth promise again to increase during the next few years. The emphasis is shifting, however, from the influence of nutrition on the development of tumors in animals to the study of factors required for the growth of neoplastic cells in tissue culture (V. J. Evans *et al., Cancer Research* **16,** *77 (1956)*; H. Eagle, *Science* **122,** *501 (1955)*; *Nutrition Reviews* **14,** *89, 154 (1956)*; P. R. White, *J. Nat. Cancer Inst.* **16,** *769 (1955)*; A. E. Pasieka, H. J. Morton, and J. F. Morgan, *Ibid.* **16,** *995 (1956)*, and others).

The importance of defining the nutritional requirements of cancer cells cannot be overemphasized. Two important problems

are dependent on the establishment of these requirements. First, cancer cells grown in culture are now being employed as test objects for the preliminary screening of cancer chemotherapy compounds. When it becomes possible to inhibit a tumor in culture with a certain compound and to reverse the inhibition by the use of another compound, the various factors involved in growth will be more clearly established and the understanding of the mechanisms involved greatly facilitated. Second, the nutritional requirements of neoplastic cells must be carefully compared with those of other rapidly proliferating cells. If some neoplastic cells can be shown to require substances which differ from those needed by normal cells, then the more or less random selection of antimetabolites for the inhibition of tumor growth will be replaced by a specifically directed approach.

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